Beneficial effect of Belatacept on health-related quality of life and perceived side-effects: results from the BENEFIT and BENEFIT-EXT trials

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Running title: HRQoL and perceived side effects of Belatacept versus cyclosporine

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AUTHOR'S CONTRIBUTIONS

FD assisted in designing the studies, interpreting the results and wrote the manuscript

SW, MY, SJ assisted in designing the studies, performed the analyses, assisted in interpreting the findings, and carefully revised the manuscript

AK assisted in designing the studies and interpretation of the findings, coordinated the trials, and carefully revised the manuscript

CONFLICT OF INTEREST STATEMENT:

FD received a consultancy fee to interpret the results of the SF-36 and MTSOSD.

SW, MY, SJ and AK are employees at BMS

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ABSTRACT

Background:

Patient reported outcomes are increasingly incorporated in drug evaluation trials. Whether new immunosuppressive drugs result in an improved health-related quality of life (HRQoL) and a reduced side effect experiences remains unknown. Moreover, the relationship between HRQoL and kidney function has never been investigated in kidney transplant recipients.

Methods:

Using the BENEFIT and BENEFIT-EXT trials, we investigated the: a) evolution of health-related quality of life (HRQoL), assessed by the SF-36 in the first 3 years (baseline, 12, 24 and 36 months) after kidney transplantation; b) association between kidney function (CKD stage), HRQoL, and patient-reported side-effects (MTSOSD-59R; BENEFIT trial only), and c) impact of belatacept and cyclosporine on side effect experience and HRQoL.

Results:

In the BENEFIT trial, all subjects reported clinically meaningful improvements compared to baseline and returned to general population scores, both for physical (PCS) and mental composite (MCS) SF-36 scores at 12 to 36 months post-Tx. In the BENEFIT-EXT trial, this was observed for PCS only. Belatacept-treated patients reported better absolute PCS scores compared to cyclosporine-treated patients. Differences were small, but statistically significant at all times. Belatacept-treated patients tended to experience

less side effects compared to cyclosporine-treated patients, except for dry skin. Worsening kidney function was associated with a significant decrease in HRQoL.

Conclusion:

Worsening in kidney function was associated with lower HRQoL. Compared to cyclosporine, belatacept was associated with improved HRQoL, suggesting that use of non-nephrotoxic immunosuppressants may affect patient's side effect experience and improve their HRQoL.

INTRODUCTION

While morbidity and mortality are the ultimate clinical endpoints of interest to transplant professionals [1], they do not fully capture the patients' perspective on how kidney transplantantation (KTx) affect their life. Patient reported outcomes (PROs) are being adopted as key parameters to fill this gap in clinical outcome evaluation and provide a more complete evaluation of medical interventions [2-5], including KTx [6].

Significant improvements in patients' health-related quality of life (HRQoL) from pre- to post-Tx have been reported consistently [1, 7]. Yet, to date, most studies focused on the early post-operative period or reported on cross-sectional comparisons of KTx with dialysis patients only [8]. Whether HRQoL is restored to a level comparable to that of healthy people and whether HRQoL gains are sustainable over the longer-term remains poorly understood. To our knowledge, no studies evaluated prospective changes in HRQoL over a relatively long post-Tx time, especially comparing distinct types of maintenance immunosuppressants.

In patients with chronic kidney disease, reduced HRQoL seems to be a hallmark of kidney failure [9, 10]. The presence of various co-morbidities as well as side effects of calcineurin inhibitors (CNIs) contribute to a reduced post-Tx HRQoL, such as nephrotoxicity, cardiovascular and metabolic problems, as well as other CNI-related side effects, such as hair growth, tremor, or muscle weakness, are not life-threatening but occur frequently and are perceived as burdensome by patients [11-13, 16]. Unfortunately,

few studies have investigated the relationship between kidney function and HRQoL in KTx recipients [14, 15].

The safety profile of CNIs underscores the need for newer immunosuppressive drugs that are able to preserve long-term kidney function, prevent non-renal toxicity and at the same time reduce the patients' perceived immunosuppressants' side effects. Recently published findings from the BENEFIT and BENEFIT-EXT trials show that KTx patients treated with belatacept, a selective costimulation blocker [17], have similar patient and graft survival rates, better renal function and improved cardiovascular and metabolic risk profiles compared to patients treated with cyclosporine [18-22]. It remains to be demonstrated, however, whether patients treated with belatacept also experience more beneficial patient reported outcomes, including HRQoL and immunosuppressants side effects experience.

This manuscript answers the following research questions:

1) What is the evolution of HRQoL in the first 3 years after KTx and do patients return to a level of HRQoL comparable to the general population?
2) What is the association between kidney function and PROs (i.e. perceived side-effects and HRQoL)?
3) Do patients treated with belatacept experience a more favorable HRQoL and fewer side effects compared to patients treated with cyclosporine at 3 years post-Tx?

RESULTS

In the BENEFIT trial (N= 666), 226 patients received LI belatacept and 221 cyclosporine treatment . In the BENEFIT-EXT trial (N= 543) 175 patients were on LI belatacept and 184 on cyclosporine treatment. Demographic and clinical characteristics are documented elsewhere [18-22].

SF-36 data at baseline, 12, 24 and 36 months follow-up were available for 91.5%, 89.3%, 92.6%, and 94.2% of the BENEFIT intention to treat (ITT) population, respectively, while 86.9%, 83.8%, 86.7%, and 86.1% of the BENEFIT-EXT ITT population completed the SF-36 at the respective time points. The MTSOSD-59R was completed by 72.5%, 69.1% and 67.3% at 12, 24 and 36 months follow-up, respectively (BENEFIT trial only).

HRQoL

Compared to baseline, all BENEFIT trial subjects reported a clinically-meaningful improvement in PCS (range: 4,8-7,0 points) and MCS (2,3-5,9 points) and reached general population norms at 12 months post-Tx (figure 1). This improvement was sustained up to 36 months post-Tx. In the BENEFIT-EXT trial, improvements were also observed, however these changes were smaller in magnitude (0.2-4.1 points for PCS and 1.5-3.6 for MCS), and the trial population reached general population age-adjusted norms for PCS only (Figure 1).

Association between HRQoL and kidney function

Patients with better kidney function had significantly better PCS and MCS than those with higher CKD-stages at all time points, except for 12-months BENEFIT and 36-months BENEFIT-EXT MCS results (see figure 2; month 36 data only).

Patient-reported side effects and their impact on HRQoL

At 12 months post-Tx, patients in BENEFIT experienced on average 20.2 different side effects, with a slight increase over time (mean = 20.9 at 24 months and 21.4 at 36 months). The most frequently experienced side effects (> 60% occurrence) at 36 months were wind (73.9%), tiredness (73%), lack of energy (63.9%) and restlessness/nervousness (63.2%) (Table 1).

Presence of a greater number of side effects was associated with lower SF-36 PCS and MCS, with differences of up to 10 points noted between Q1 and Q4 at all follow-up points (Figure 3).

Several side effects had a large and clinically-meaningful impact on PCS and MCS at 36 months post-Tx, whereas absence of side effects yields HRQoL scores close to those of a normal population (Table 1). The largest differences in PCS between patients experiencing versus not experiencing a given side effect were noted for breathlessness (8.2 points), altered voice (7.8), lack of energy (7.4) muscle weakness (7.3), and joint pain (6.1). For MCS, the largest differences were found for depressed mood (14.1 points),

anxiety (11.9), restlessness (10.6), mood swings (10), stomach complaints (9.4) and lack of energy (9.4).

Impact of belatacept on HRQoL

Belatacept-treated patients reported better absolute PCS. Absolute PCS differences between groups were small (1.7-2.1 points in the BENEFIT trial and 2.3-2.8 in the BENEFIT-EXT trail), but statistically significant and clinically meaningful on all comparisons (Figure 1). There was no difference between groups for MCS.

Impact of belatacept on patient-reported side-effects

The number of side effects experienced was significantly lower for the belatacept LI group compared to the cyclosporine group at all follow-up times (Figure 4).

A difference in occurrence of at least 5% was reported for 21 side effects, with the following 11 side effects occurring less frequently in belatacept-treated patients: oily skin, trembling hands, face/back spots, swollen gums, swollen ankles/feet; tingling/numbness of fingers or hands; increased hair growth, muscle weakness, lack of energy, muscle cramps and shortness of breath. Dry skin was the only side effect that was reported more frequently in the belatacept group.

Patients on belatacept also reported less distress from side effects, yet differences did not reach statistical significance (data not shown).

DISCUSSION

PROs have started to play a prominent role when evaluating new drug therapies for patients with chronic conditions [2-6]. Analyses of the BENEFIT and BENEFIT-EXT PRO data revealed that 1) HRQoL improved from pre- to post-Tx, with the beneficial effects sustained up to 3 years post-KTx; 2) worsening kidney function is associated with a significant decrease in HRQoL; and 3) patients treated with belatacept tended to experience less side effects compared to cyclosporine treated patients.

The observed HRQoL improvement from pre- to post-Tx is not surprising: There is an almost 100% consensus that HRQoL is better in KTx patients than their dialysis counterparts [1, 7, 25, 30]. Yet, given that both groups are typically compared by using cross-sectional designs, differences could likely in part be explained by older age and higher co-morbidity in dialysis patients [1, 7, 25]. Our study was able to overcome these biases by using a prospective repeated-measures design, allowing us to observe long-term evolutions in HRQoL within the same cohort and to compare the effect of different treatment regimens on HRQoL. Our pre- to post-Tx improvements in the BENEFIT trial were consistent with the 5-7 point differences seen in cross-sectional studies [25]. In BENEFIT-EXT, HRQoL improvements were smaller, but also significant and clinically relevant (i.e. an incremental 2-3 points change in PCS in addition to improvements seen post-Tx in general). To our knowledge, no other immunosuppressive drug testing trial has been able to demonstrate this. Improvements in MCS were less prominent, which is consistent with previous HRQoL studies that predominantly found physical functioning

improvements also [1, 7, 25]. . Interestingly, our post-Tx SF-36 scores are similar to those of a healthy population, underscoring that KTx is capable of restoring close to normal functioning in most patients [23, 24]. The fact that the majority of patients underwent deceased donor KTx and completed the baseline questionnaire post-Tx based on their pre-Tx memories might explain why baseline scores were relatively high.

In addition, we found a graded pattern of reduced HRQoL with worsening kidney function, illustrating that HRQoL is not a trivial outcome for patients with chronic kidney disease. With the exception of one cross-sectional study [15], we are not aware of other prospective studies showing that patients in CKD stage 4 and 5 experience a significantly reducted HRQoL. Evidence suggests that a PCS below 43 is indicative of perceived problems that might impede life functioning [31]. Our observations for patients in stage 4 and 5 are therefore particularly worrisome and underscore the need for renal sparing programs or therapeutic options that are able to reduce nephrotoxicity.

In line with the systematic review of Kugler et al. [16], we found that patients who experienced more side effects had a reduced HRQoL. Impact on MCS was particularly noted for emotion-related side effects, like depression, anxiety, or restlessness. Appropriate interventions might not only reduce these side effects, but segue into a better HRQoL, a hypothesis that merits further testing.

Compared to cyclosporine-treated patients, the belatacept group showed significantly better PCS in both trials and at all follow-up points, while differences for MCS were not

statistically significant. Although both trials consistently show better preserved kidney function when treated with belatacept [18-22], we don't know if better PCS in the belatacept groups can be explained by a slower decline in kidney function over time, as unfortunately numbers were too small to make meaningful comparisons in HRQoL as a function of CKD stage between treatment arms.

Another explanation for the higher HRQoL scores in belatacept-treated patients might be found in a more beneficial side effect pattern. Relative to belatacept, patients treated with cyclosporine experienced on average 3 more symptoms. Moreover, eleven symptoms were significantly more reported, like tremor, gum growth, muscle weakness or excessive hair growth. These are consistently ranked among the top 10 most frequently reported side effects across studies that include either patients on cyclosporine or tacrolimus [16]. Dry skin was the only side effect that belatacept-treated patients reported more frequently. Whether these observed side effect profiles would continue to be favorably in belatacept- versus tacrolimus-based or other immunosuppressive regimens is unknown. In contrast to documentation of adverse events, there is a paucity of studies comparing subjective side effect experiences between treatments. A recent study showed that switching patients from cyclosporine- to tacrolimus seem to alleviate occurrence and burden of cosmetic effects attributable to cyclosporine such as hypertrichosis and gingival hyperplasia. An additional gain of belatacept- versus CNI-based regimens remains to be demonstrated [32]. Nevertheless, our findings suggest that evaluation of subjective symptom experience might be valuable when professionals select immunosuppressive regimens, as patients experience many side effects that are not

harmful, but could be distressing and negatively impact their HRQoL. In fact, multiple guidelines underscore the relevance of incorporating PROs in selecting treatments or when making treatment decisions [2-5].

Strengths of this paper include the large sample size and the 3 years prospective follow-up. A first limitation is the reliance on PRO instruments that might not be ideally suited for Tx populations. While there are a number of HRQoL instruments that have been used in Tx before, Butt and colleagues [33] in their systematic review concluded that none can be considered the gold standard and that the SF-36 was by far the most frequently used instrument KTx. Similarly, although other self-report instruments exist to measure perceived side effects, the MTSOSD equals or exceeds the reliability and validity of other instruments. Moreover, the MTSOSD-59R is the only PRO that is validated for use in newer immunosuppressive regimens, including belatacept. Secondly, our baseline assessment might not reflect actual HRQoL prior to Tx, as deceased donor KTx patients completed the questionnaires post-Tx. This might have introduced a recall bias, yet, post-hoc analyses did not find significant differences in HRQoL scores between those who completed the questionnaire 4 weeks prior versus post-Tx. Thirdly, as for all HRQoL studies, we only have information about included patients, which might have introduced a selection bias and overestimation of post-Tx HRQoL. It is for instance possible that patients who discontinued trial participation because of death (N= 3 in the BENEFIT and N= 17 in BENEFIT-EXT trial [22, 36]) might have had a poorer HRQOL. Yet, we compared our ITT population with those completing the study, and found similar results. Similarly, although our HRQoL results at group level are comparable to that of healthy

controls, individual KTx patients might have suboptimal scores that remain invisible by the nature of our analyses. Patients who developed post-transplant lymphoproliferative disorder (PTLD) for instance, might have experienced a lower quality of life, yet numbers were too small (i.e. 11 cases at 3 years follow-up in both trials spread over the 3 treatment arms) to conduct meaningful statistical comparisons [22; 36]. Likewise, too few patients died in both trials, rendering comparisons between survivors and non-survivors difficult. Fourthly, although more than 85% of patients completed the SF-36 at each time point in both trials, only about 70% of the ITT population completed the MTSOSD, possibly because no culturally sensitive translations were available for specific countries, like e.g. Argentina, Mexico, or Czech Republic. The MTSOSD was used in the BENEFIT trial only, hence no information is available on side effect experience in the extended criteria donors KTx group. Finally, only comparisons with cyclosporine-treated patients were made, making it unclear how patients treated with different immunosuppressive regimens relative to belatacept would rate their HRQoL and symptom experience over time, representing interesting avenues for further research. Studies comparing tacrolimus-based regimens with cyclosporine [34] or tacrolimus-free regimens [35] for instance found differences in SF-36 PCS of 1.3 and 3 points in favor of tacrolimus, respectively.

Given that lower levels of kidney function (CKD stages 4 and 5) were associated with a significant lower HRQoL, and that lower CKD was more common in cyclosporine-treated patients, our findings suggest that use of non-nephrotoxic immunosuppressant agents might have benefits beyond renal function. Appropriate selection of

immunosuppressant regimens should consider not only kidney function and survival but also the patients' overall HRQoL.

MATERIALS AND METHODS

Design and sample

The methodology of the BENEFIT and BENEFIT-EXT trials is described in detail elsewhere [18-22]. In brief, BENEFIT is a 3-year, randomized, active-controlled parallel group, multicenter Phase III study conducted at 100 centers worldwide. Eligible adult patients having received a living donor or standard criteria deceased KTx were randomized 1:1:1 into a more intensive (MI) regimen of belatacept; a less intensive (LI) belatacept regimen or cyclosporine for primary maintenance immunosuppression. All patients were also treated with basiliximab induction, mycophenolate mofetil and corticosteroids.

BENEFIT-EXT is a 3-year, randomized, multicenter study in adult patients from 79 centers who received an extended criteria donor KTx. Patients were randomized into a MI or LI belatacept treatment group or cyclosporine. Unless specified otherwise, for most analyses, only data for the belatacept LI group will be presented, given that this regimen has been approved for use in clinical practice.

Measurements

HRQoL

The Short Form Health Survey (SF-36 v2) is a widely used generic self-report instrument to assess HRQoL that is validated for use in patients with kidney disease, including Tx

[23-25]. Patients completed the SF-36 at baseline (within 30 days of Tx), at 12, 24 and 36 months after KTx. Given that the Tx date in case of deceased donor Tx is not known in advance, patients were allowed to complete the baseline questionnaire post-Tx based on their recollection of their HRQoL in the 4 weeks preceding Tx.

The 36 Likert-type questions are classified into 8 subscales, which are summarized into a physical composite score (PCS) and mental composite score (MCS) that are transformed to norm-based scores with mean of 50 and standard deviation of 10. For the BENEFIT trial, a mean of 50±3 represents a PCS or MCS that is comparable to that of the general population. For BENEFIT-EXT, age-adjusted norms were used, given that subjects were slightly older,, with a PCS of 47 and a MCS of 52 reflecting a HRQoL comparable to age-adjusted general population norms [24]. A 2-point difference in PCS and a 3-point difference in MCS are considered as clinically meaningful [23, 24].

Side effect experience

The Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R), consists of 59 side-effects that patients might experience while taking immunosuppressive medications [26]. *Side effect occurrence* is measured in terms of frequency or severity, while *symptom distress* encompasses mental anguish or suffering caused by a specific immunosuppressant side-effect [27].

Patients rate each side-effect on a five-point scale, ranging from 0 (never) to 4 (always occurring) for occurrence, and from 0 (not at all distressing) to 4 (extremely distressing)

for distress. This scale has been validated to measure side-effects of current and newer immunosuppressive drugs, including belatacept [26]. Patients completed the MTSOSD-59R at 12, 24 and 36 months in the BENEFIT trial only and in countries for which a culturally sensitive translation was available. No baseline measure was completed, given that patients were not yet on immunosuppressants treatment pre-Tx

Kidney function

Calculated GFR (cGFR) in mL/min/1.73 m^2 was determined at baseline, 12, 24 and 36 months post-Tx using the Modification of Diet in Renal Disease (MDRD) equation [28] and the chronic kidney disease (CKD) stage 1 to 5 classification [29].

Statistical analysis

The analyses focus on the HRQoL, side effect experience, and renal function data only. The intention-to-treat (ITT) analyses for the primary and secondary clinical efficacy outcomes are reported elsewhere [18-22]. Descriptive statistics are presented as appropriate. In the case of missing data, the last observation was carried forward.

Norm-based SF-36 v2 subscale scores, as well as physical composite (PCS) and mental composite (MCS) absolute scores and change in scores were compared at 12, 24 and 36 months post-, using ANOVA.

Absolute PCS and MCS were compared between CKD stages 1 to 5 at 12, 24 and 36 months post-Tx, using ANOVA. Stage 1 and 2, as well as stage 4 and 5 were grouped because of the small number of patients especially in the more advanced kidney failure stages.

Differences between belatacept LI and cyclosporine-treated groups norm-based SF-36 v2, subscales, PCS and MCS absolute scores relative to pre-Tx were compared at baseline, 12, 24 and 36 months, using ANOVA.

Symptom frequency between both groups was compared by independent student's t-testing. Scores per symptom were dichotomized first as "symptom not experienced" (MTOSD-59R score = 0) versus "symptom occurring" (MTOSOSD-59R scores 1, 2, 3 or 4) and summed. For distress, mean scores were calculated. Total number of side effects experienced were also divided into quartiles (Q1-Q4), allowing comparison of PCS and MCS between quartiles at the different time points, using ANOVA.

Data were analyzed using SAS 9.2. Statistical significance was set at $p< 0.05$.

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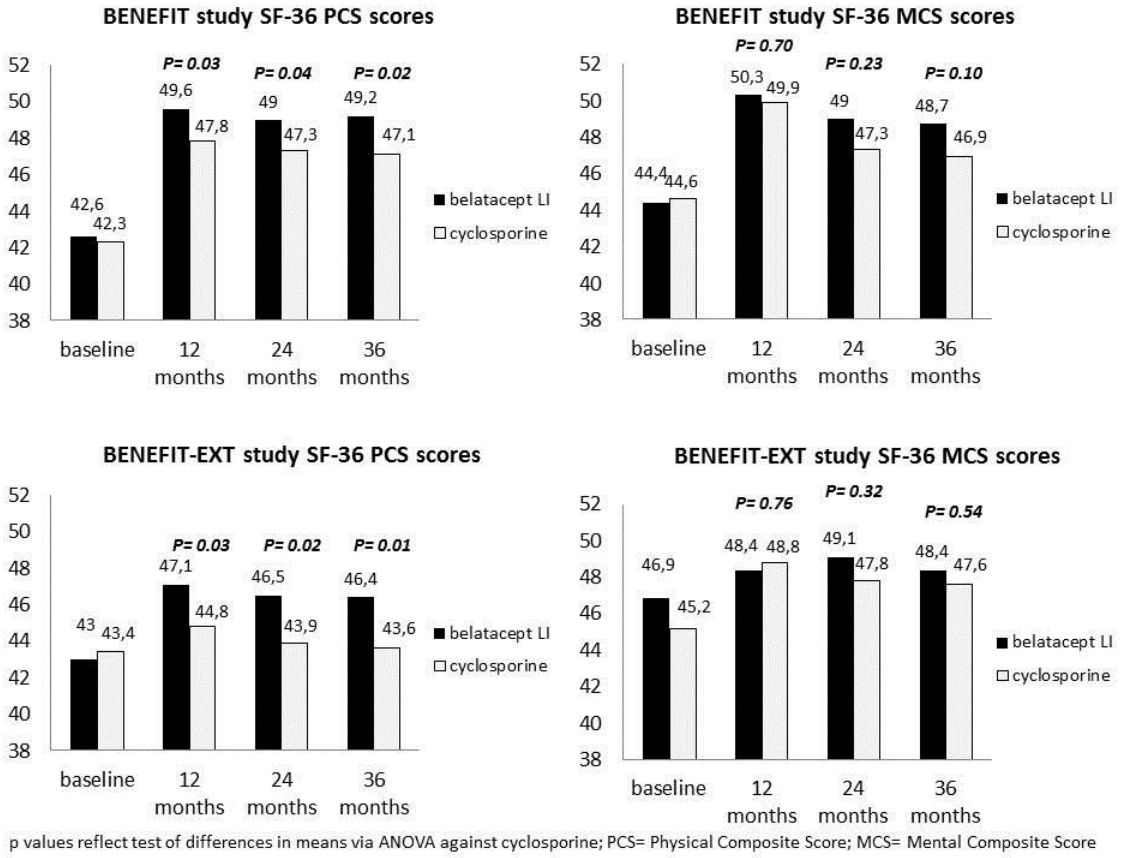
Table 1: prevalence of experienced side effects and their impact on Physical Composite score (PCS) and Mental Composite Score (MCS) at 36 months post-transplant in BENEFIT trial

		Physical composite score (PCS)			Mental Composite Score (MCS)		
Side effect as assessed by MTSOSD-59R	**% of patients in which side effect is occurring**	**PCS if Side effect absent**	**PCS if Side effect present**	**Absolute difference in PCS**	**MCS if Side effect absent**	**MCS if Side effect present**	**Absolute difference In MCS**
Warts on hands or feet	7,4%	48,7	47,8	0,9	48,3	45,4	2,9
Warts around genitals	7,5%	48,7	47,5	1,2	48,3	44,7	3,6
Swollen glands in neck, armpit or groin	7,9%	48,7	47,9	0,8	48,5	43,1	5,4
Altered voice	11,1%	49,5	41,7	7,8	48,8	41,8	7,0
Fat deposits on neck and back	12,3%	48,8	47,7	1,1	48,9	42,3	6,6
Swollen gums	15,3%	48,7	48,4	0,3	48,7	44,4	4,3
Abnormal skin color	15,4%	49,4	44,6	4,8	49,3	41,1	8,2
Larger breasts	16,7%	49,0	46,7	2,3	48,7	45,1	3,6
Changed taste	17,9%	49,6	44,3	5,3	49,4	42,2	7,2
Skin rash	20,7%	49,0	47,0	2,0	48,8	45,2	3,6
Low appetite	21,9%	49,8	45,7	4,1	49,6	44,0	3,6
Redness of face and neck	22,1%	49,2	46,7	2,5	48,9	45,3	3,6
Changed facial features	22,1%	49,4	46,0	3,4	49,8	42,0	7,8
Chest pain	22,3%	49,6	45,2	4,4	49,8	42,3	7,5
Brittle nails	24,2%	49,3	46,4	2,9	48,5	46,8	1,7
Puffy face (moon face)	24,6%	49,5	45,9	3,6	49,5	43,7	5,8
Sores on lips or in mouth	25,6%	49,0	47,7	1,3	49,2	44,9	4,3
Feeling of warmth in hands or feet	25,8%	49,4	46,4	3,0	49,3	44,7	4,6
Hearing loss	26,7%	49,8	45,4	4,4	49,2	45,1	4,1
Stomach complaints or nausea	28,1%	50,1	44,7	5,4	50,7	41,3	9,4
Palpitations	30,2%	49,9	45,7	4,2	49,8	44,2	5,6
Increased hair growth	30,9%	48,8	48,3	0,5	48,7	46,8	1,9
Nightmares	31,2%	50,0	45,6	4,4	50,8	42,0	8,8
Brittle skin	31,4%	49,8	46,0	3,8	49,7	44,6	5,1
Oily skin	31,9%	48,7	48,5	0,2	48,5	47,2	1,3
Spots on face and/or back	32,6%	48,5	48,9	-0,4	49,2	45,8	3,4
Constipation	35,3%	49,8	46,3	3,5	49,7	45,0	4,7
Menstrual (female) / erectile problems (men)	36,0%	49,6	46,8	2,8	49,4	45,7	3,7

Breathlessness	36,0%	51,2	44,0	8,2	50,3	44,1	6,2
Swollen ankles	37,2%	50,3	45,8	4,5	49,2	46,3	2,9
Muscle cramps	37,5%	50,3	45,8	4,5	50,0	44,8	5,2
Tingling or numbness in hands or feet	38,6%	50,2	46,1	4,1	49,8	45,3	4,5
Itching	39,5%	49,8	46,8	3,0	49,5	45,9	-0,4
Hair loss	39,5%	49,0	48,1	0,9	49,1	46,5	2,6
Diarrhea	40,0%	49,6	47,1	2,5	49,8	45,4	4,4
Dizziness	40,2%	50,7	45,5	5,2	50,9	44,0	6,9
Trembling hands	40,9%	50,4	46,1	4,3	50,3	44,8	5,9
Dry skin	43,0%	49,6	47,3	2,3	49,2	46,5	2,7
Blurred vision	43,3%	50,4	46,3	4,1	50,4	45,1	5,3
Easy bruising	43,7%	50,6	46,1	4,5	50,0	45,6	4,4
Reduced interest in sex	44,9%	50,8	45,9	4,9	51,3	44,1	7,2
Increased urge to urinate	45,4%	50,1	46,9	3,2	49,9	45,9	4,0
Increased sensitivity to light	45,6%	50,1	46,8	3,3	50,3	45,5	4,8
Depressed mood	46,0%	50,9	45,9	5,0	54,5	40,4	14,1
Muscle weakness	47,0%	52,1	44,8	7,3	52,2	43,5	8,7
Increased sweating	47,2%	49,2	47,9	1,3	49,9	46,1	3,8
Join pain	48,2%	51,6	45,5	6,1	50,1	45,9	4,2
Anxiety	48,9%	50,7	46,4	4,3	53,9	42,0	11,9
Concentration or memory difficulties	49,5%	50,7	46,5	4,2	51,2	44,9	6,3
Headaches	50,4%	49,9	47,4	2,5	51,0	45,2	5,8
Back pain	52,8%	51,4	46,2	5,2	51,9	44,7	7,2
Increased thirst	53,5%	50,2	47,3	2,9	49,7	46,7	3,0
Sleep problems	54,7%	50,9	46,8	4,1	51,5	45,3	6,2
Mood swings	56,0%	51,1	46,7	5,4	53,7	43,7	10,0
Increased appetite	58,4%	49,4	48,1	1,3	49,5	47,1	2,4
Restlessness / nervousness	63,2%	51,0	47,2	3,8	54,8	44,2	10,6
Lack of energy	63,9%	53,4	46,0	7,4	54,1	44,7	9,4
Tiredness	73,0%	53,0	47,1	5,9	53,3	46,0	7,3
Increased wind	73,9%	50,0	48,1	1,9	49,9	47,5	2,4

MTSOSD-59R: Modified Transplant Symptom Occurrence and Symptom Distress Scale (59 items revised version)

OVERVIEW OF FIGURES



p values reflect test of differences in means via ANOVA against cyclosporine; PCS= Physical Composite Score; MCS= Mental Composite Score

Figure 1: SF-36 Physical Composite Score (PCS) and Mental Composite Score (MCS) for belatacept LI and cyclosporine groups

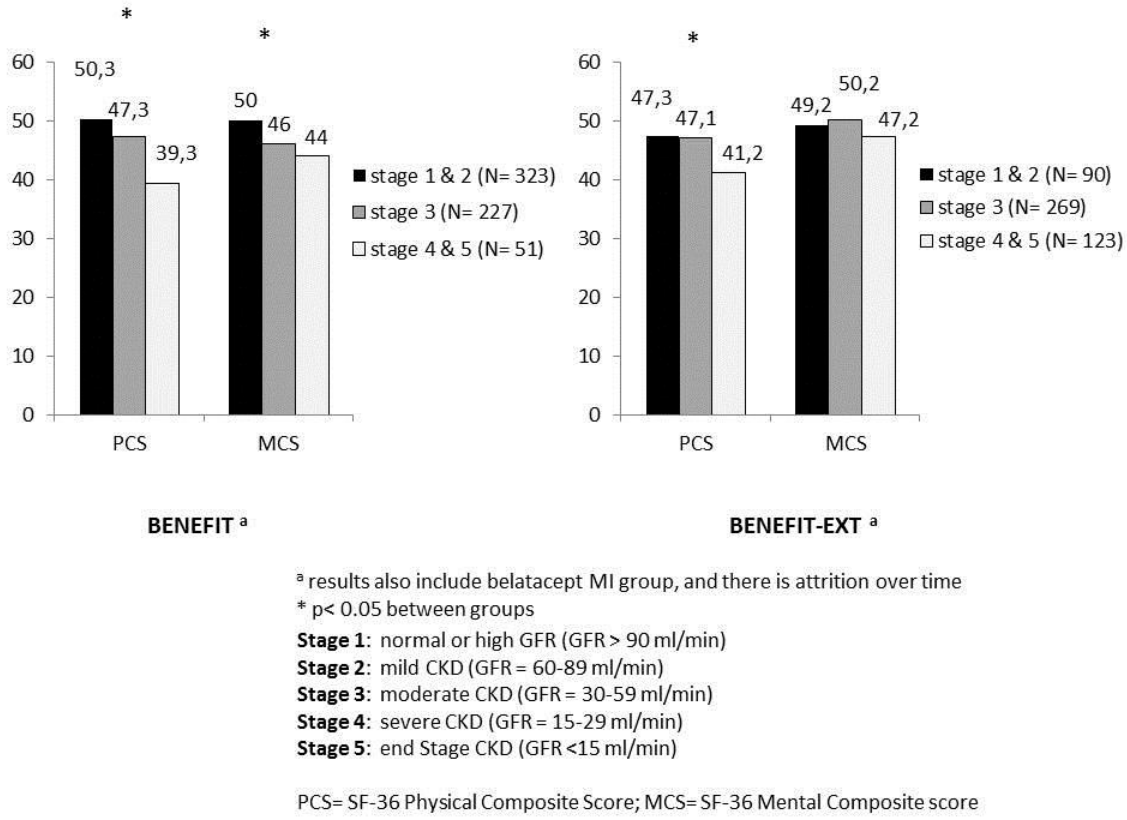


Figure 2: Association between Health-related quality of life (HRQoL) and Chronic Kidney Disease (CKD) stage at 36 months post-Tx

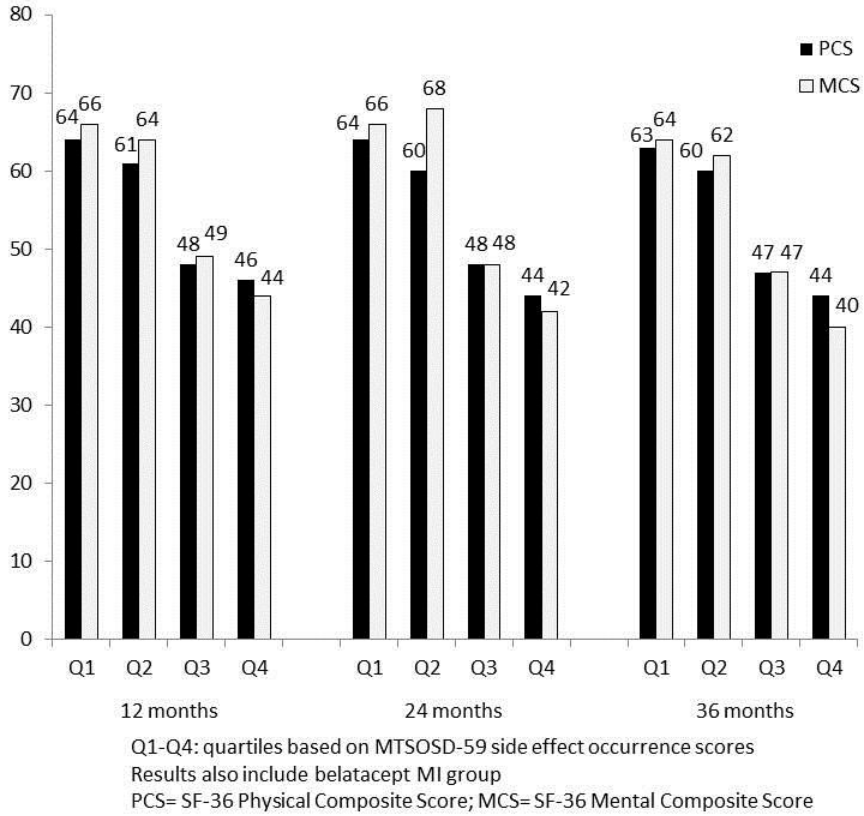


Figure 3: Association between Health-related quality of life (HRQoL) and occurrence of side effects

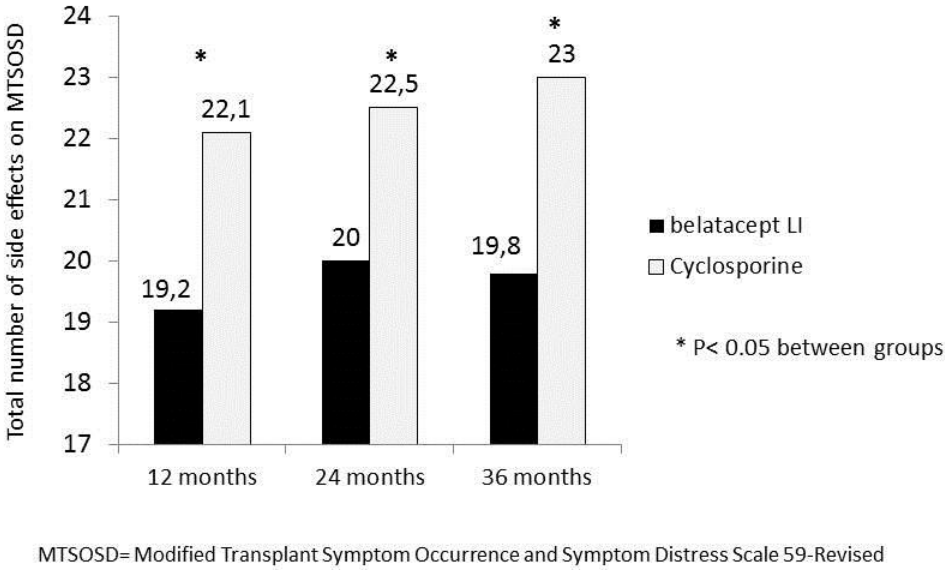


Figure 4: Comparison of total number of side effects between belatacept LI and cyclosporine groups